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EXAMINER	
KUSHAN, J	
ART UNIT	PAPER NUMBER
186	16

DATE MAILED: 04/06/89

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

[X] This application has been examined [X] Responsive to communication filed on 12/9/88 and 12/22/88 [X] This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. [ ] Notice of References Cited by Examiner, PTO-892.
2. [ ] Notice re Patent Drawing, PTO-948.
3. [X] Notice of Art Cited by Applicant, PTO-1449
4. [ ] Notice of Informal Patent Application, Form PTO-152
5. [ ] Information on How to Effect Drawing Changes, PTO-1474
6. [ ] _____

Part II SUMMARY OF ACTION

1. [X] Claims 17 to 20 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. [X] Claims 1 to 16 have been cancelled.
3. [ ] Claims _____ are allowed.
4. [X] Claims 17 to 20 are rejected.
5. [ ] Claims _____ are objected to.
6. [ ] Claims _____ are subject to restriction or election requirement.
7. [ ] This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.
8. [ ] Allowable subject matter having been indicated, formal drawings are required in response to this Office action.
9. [ ] The corrected or substitute drawings have been received on _____. These drawings are [ ] acceptable; [ ] not acceptable (see explanation).
10. [ ] The [ ] proposed drawing correction and/or the [ ] proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been [ ] approved by the examiner. [ ] disapproved by the examiner (see explanation).
11. [ ] The proposed drawing correction, filed _____, has been [ ] approved. [ ] disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.
12. [ ] Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [ ] been received [ ] not been received [ ] been filed in parent application, serial no. _____; filed on _____.
13. [ ] Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. [ ] Other

15. The text of those sections of Title 35, U.S. Code not included in this actions can be found in a prior Offic action.

16. Claims 17 to 20 are pending. Claims 18 and 19 are directed to a factor IX protein having the following submitted properties;

a) is between 90 and 100% biologically active with respect to factor IX present in normal human plasma,

b) is derived from a single human individual,

c) has an amino acid sequence sufficiently similar to, or identical to native human factor IX,

d) is "free" from contamination by poxviruses and by plasma constituents.

Claims 19 and 20 are directed to a method for treating factor IX deficiency in a human patient comprising administering the factor IX defined above.

17. The declarations under 37 CFR 1.132 filed as paper no. 14 is insufficient to overcome the rejection of claims 17 to 20 based upon 35 USC 102/103 as set forth in the last Office Action because the declarations do not establish that the product as disclosed differs from the factor IX products known in the art. All three declarations attest to the

difficulties in producing biologically active factor IX. The examiner appreciates the difficulty of finding an appropriate host cell which will be able to carry out the post-translational modifications (e.g. the gamma-carboxylation and b-hydroxylation of the appropriate residues) and to produce fully active factor IX in a recombinant procedure. The opinions of the three inventors are well taken with respect to difficulties involved in a recombinant process of making factor IX. These opinions, however, are not sufficient to overcome rejections of the product claimed.

18. Claims 17 and 18 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Osterud et al, or Suomela et al.

As set forth in the first office action, the product claims presented by applicant define human factor IX which are anticipated by the cited prior art. Applicant, in response to the prior action, has submitted declarations which attest to the difficulties in producing biologically active factor IX by recombinant techniques. Further, applicant has submitted a response to the rejection which presents the following points;

a) the teachings of the prior art do not show how to remove high molecular weight plasma contaminants from factor IX,

b) the factor IX products known in the art are contaminated with high molecular weight plasma contaminants,

c) the reference to poxvirus contaminations is relevent to other recombinantly derived factor IX products which have been produced via a vaccinia-virus based transfection procedure,

d) when factor IX is derived from traditional purification procedures, (i.e., non-recombinant) a polymorphism in a single amino acid residue position exists, and that this polymorphism indicates that factor IX produced by a recombinant process is distinct from such a polymorphically derived native factor IX product.

The response to the first office action, based on the above points, and based on the declarations submitted is not sufficient to overcome the rejections of record.

A review of the art cited against applicant is appropriate here. In Osterud et al, the authors teach purification of factor IX to a degree that indicates that it is in fact a homogeneous protien free of high molecular weight contaminants. Applicant is directed to figure 2, page 5949, which shows a single band on SDS-PAGE. There are no contaminating proteins in this preparation. The isolated factor IX was fully active, as indicated at the top left of

page 5949. Also note figure 3, which summarizes the activity of the purified factor IX. In figure 4, the conversion of factor IX into factor IXa is documented. Note especially that the small "tail" appearing after the sharp factor IX peak in the top profile of figure 4 grows with time in the next two profiles in figure 4. Note especially that this tail corresponds to one of the breakdown products of factor IX.

Suomela et al teach production of homogeneous human factor IX. At page 149, these authors demonstrate the homogeneity via PAGE, SDS-PAGE, ultracentrifugation, and by raising monospecific antiserum to the purified factor IX. Suomela et al also state that degradation products comprising less than 5% of the total protein were observed in later SDS-PAGE analysis, after the product had been frozen and thawed. The highlighted portion of page 149 indicates that a new N-terminal amino acid residue can be observed after freezing and thawing, presumably arising by self-activation of factor IX. At page 150, applicant has pointed to the observed microheterogeneity of the purified factor IX when analyzed by isoelectric focusing under a very narrow pH range of ampholytes. Under these narrow conditions, four isolectric components could be observed. Using a steeper, and more conventional pH gradient one peak was observed.

In both Osterud et al, and in Suomela et al, homogeneous human factor IX was produced. Applicants assertions that the techniques disclosed do not separate out high molecular weight components associated with factor IX are unsupported by evidence. Both disclosures cited show that the factor IX produced is homogeneous according to several analytical procedures. Nothing in these disclosures would lead one to believe that the factor IX preparations are contaminated by high molecular weight impurities.

Applicant is also reminded that factor IX is a proenzyme, which can undergo self-activation to produce a number of degradation fragments, one of which being active factor IXa. Especially relevent is the fact that one fragment is a 44 k.D. species (e.g. a "high molecular weight protein contaminant"). Osterud noted that the fragments appeared after freezing/thawing or extended storage of the purified homogeneous factor IX. Suomela et al indicate that four isoelectric peaks can be observed under certain conditions, but note that approximately four degradation products are observed after self-degradation of the factor IX preparations of Osterud et al. In all likelyhood, the "high molecular weight contaminants" alleged by applicant are probably degradation products of factor IX which arise when the factor IX is converted into active factor IXa. But bear

in mind that applicant has not proven that these "contaminants" do in fact exist.

If applicant's recombinant factor IX were analyzed using the same analytical procedures taught by the cited prior art, it would be more likely than not that identical results would be observed. Applicant has not submitted such a comparison. Especially relevent is the absence of any comparison of the recombinant factor IX to the homogeneous preparations of the prior art. If applicant's factor IX is at least 90% active (which it apparently is) then the same degradation product "contaminants" will be observed. In any case, applicant has not submitted any evidence which proves that the recombinant product is different by any measure from the conventionally produced factor IX taught by the cited art.

The limitation concerning the presence of poxviruses is irrelevent to an argument of distinction over the conventionally produced factor IX. This limitation does not distinguish the claims over the cited art.

Applicant has asserted that a polymorphism exists in factor IX which is purified from pooled human plasma. Note that this argument does not point to an actual distinction over factor IX produced from pooled human plasma as opposed to recombinant factor IX, but implies that there is a possibility that the recombinant factor IX will differ in part from the factor IX derived from pooled human plasma.

The recombinant factor IX does not introduce a novel amino acid residue at the alleged polymorphic residue location. The recombinant protein allegedly has only one possible amino acid at this site, rather than one out of possibly two residues. An argument based on a potential difference at one amino acid site cannot possibly be considered to be persuasive. Applicant does not even show that the polymorphism in fact is relevent to the teachings applied against the claims (e.g. applicant has not shown that the potential polymorphism occurred in the factor IX preparations of the prior art). Applicant has not proven that a distinction in fact exists between the factor IX produced by the cited prior art and that instantly claimed.

Next, applicant's claims which state that the recombinant protein is derived from a single human source, yet may include any species of factor IX which has an amino acid sequence sufficiently similar to factor IX to make it acceptable for infusion into human patients by itself defeats the premise of the polymorphic residue site argument. Applicant is in effect saying that because the conventionally produced factor IX may have a percentage of a species of factor IX which is not identical to the recombinant species that the recombinant species is patentably distinct, but his invention should encompass any and all modifications of factor IX which result in a biologically active factor IX.

Thus, a species which differs at several amino acid residue locations but which is still acceptable for infusion into humans would be encompassed by the claims, but the fact that the naturally derived species of factor IX which may differ at one site, and is otherwise identical should be considered to be a patentably distinct species from the recombinant species. Applicant is reminded that the conventionally produced species of factor IX are acceptable for infusion into humans. On its face, the argument in view of applicant's claims is incongrous.

Applicant has not indicated that the polymorphism leads to any discernable distinction between the two factor IX homologs which differ at a single amino acid site. The two potential amino acid residues do not differ materially--substituting one for the other would not be expected to produce any detectable difference. An argument that the protein produced recombinantly which may differ from a conventionally produced factor IX by a single undetectable amino acid substitution should be deemed to be patentably distinct over said conventionally produced protein is untenable.

Applicant has not met his burden of proving that a distinction exists from the claimed protein over the cited prior art. As such the rejection as stated in the first

office action is maintained over Suomela et al or Osterud et al.

19. Claims 17 to 20 are rejected under 35 U.S.C. 103 as being unpatentable over Suomela et al or Osterud et al in view of Schwinn et al.

The claims directed to a method of treating factor IX deficiencies are newly presented.

As shown above, the factor IX preparations of Osterud et al and of Suomela et al are identical to the recombinant factor IX of applicant. What is not explicitly taught by these disclosures is the preparation and adminstration of pharmaceutically acceptable doses of factor IX. The authors make clear in both of these disclosures that the purpose of their purification of factor IX is to provide factor IX preparations which can be used to treat factor IX deficiencies.

The disclosure of Schwinn et al teaches how to sterilize and prepare factor IX for infusion into human patients which have factor IX deficiencies. At columns 3 and 4 of Schwinn et al, the ordinary worker is clearly shown how to prepare and adminster pharmaceutically acceptable preparations of factor IX.

A method of treating factor IX deficiency by adminstering factor IX (recombinant or conventionally

produced) would have been immediately apparent to the ordinary worker in this field prior to applicant's earliest priority date. The claimed method simply recites administration of the factor IX preparation. Schwinn et al teach the method using apparently non-homogeneous solutions of factor IX, but the fact that potential impurities are made safe via sterilization/pasteurization is relevent. Furthermore, prior to applicant's earliest priority date, highly purified factor IX preparations (e.g. identical to the recombinant factor IX claimed) were available, and were clearly stated to be useful in treating factor IX deficiencies. Thus, the ordinary worker, equipped with the cited disclosures, would have found the instantly claimed procedure immediately suggested by said art. As such, the method as claimed would have been prima facie obvious to said worker at the time of applicant's filing.

20. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED

STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

21. The rejections over Anson et al, Fujikawa et al, Anderson et al, and Schwinn et al are withdrawn. These disclosures do not show preparation of highly purified human factor IX. Anson et al is not prior art to the instant application. The amendments to the claims obviates the bases for rejection over 35 USC 112.

22. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 180, Art Unit 186.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeff Kushan whose telephone number is (703) 557-7627. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 557-0664.

jpk
March 25, 1989.

MARGARET MOSKOWITZ
SUPERVISORY
PATENT EXAMINER
ART UNIT 186